AF/1642 IFW

BEFORE THE BOARD OF APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Raulet et al.	Group Art Unit: 1642
Serial No. 09/871,491	Examiner: Harris, Alana M.
Filed: May 31, 2001	Attorney Docket No. B01-088
For: *Tumor Therapy*	CERTIFICATE OF MAILING I hereby certify that this corr. is being deposited with the US Postal Service as First Class Mail in an envelope addressed to the Comm. for Patents, PO Box 1450, Alexandria, VA 22313-1450 on June 3, 2004. Signed _____ Richard Osman

BRIEF ON APPEAL

The Honorable Board of Appeals and Interferences
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Honorable Board:

This is an appeal from the Feb 24, 2004 final rejection of claims 39, 45, 51 and 53. As a matter of context, this is the *fourth, consecutive action on the merits* in this application.

REAL PARTY IN INTEREST

The real parties in interest are The Regents of the University of California, and Innate Pharma Inc., the assignee and licensee, respectively, of this invention.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals or interferences.

STATUS OF THE CLAIMS

Claims 39, 45, 51, and 53 are pending and subject to this appeal.

STATUS OF THE AMENDMENTS

All Amendments are believed to be properly before the Board.

SUMMARY OF THE INVENTION

Natural killer (NK) cells attack many tumor cell lines in vitro, and, after activation, can attack primary tumor cells. NK cells have therefore long been thought to be involved in tumor surveillance and to be an important part of anti-tumor immunity, but the basis for the interaction between NK cells and tumor targets remains largely unknown. Recently, the stimulatory lectin-like NKG2D receptor has been characterized. In mice, the receptor is expressed by NK cells, activated CD8+ T cells and activated macrophages, and receptor engagement can stimulate or costimulate these cells. Several distinct families of cell surface ligands for NKG2D have been identified, all of which are distantly related to class I MHC molecules. These ligands are often expressed at high levels by tumor cells, but not by normal cells in mature animals. While the prevalence of these ligands on highly tumorigenic cells suggests they might provide a target for therapeutic intervention, it also suggested that their presence is insufficient to provoke a host rejection of the tumor. Specification, p.1, lines 16-27.

The inventors disclose the remarkable development of methods whereby, contrary to expectations, NKG2D ligands can indeed be exploited to provoke a host response to inhibit tumor growth. Their methods are also effective prophylactically, to inhibit tumor formation, and remarkably, are effective against both tumors expressing the ligands and tumors which do not. Specification, p.1, lines 28-32; Specification Examples, p.11, line 5 - p.26, line 13.

There are only two independent claims. Claim 39 is limited to a method for inhibiting prostate tumor growth in a mammalian host determined to have a metastatic prostate tumor and comprising prostate tumor cells expressing native NKG2D, by: (a) administering to the mammalian host a composition comprising an NKG2D-binding agent, wherein the NKG2D-binding agent is multivalent and comprises a plurality of non-covalently linked NKG2D-binding moieties of natural NKG2D ligands, wherein the moieties are restricted to a common presenting surface, wherein the common presenting surface is of a host-compatible cell transduced to express the binding moieties, wherein the natural NKG2D ligands are selected from the group

consisting of MICA, MICB and ULBP, wherein the administering step is effective to inhibit growth of the tumor; and (b) detecting a resultant inhibition of growth of the tumor by evaluating growth of the tumor. Specification, claim 39.

Independent claim 51 is identical to claim 39 except that it specifically targets a primary mammary tumor growth in a mammalian host determined to have a primary mammary tumor and comprising mammary tumor cells expressing native NKG2D. Claims 45 and 53 restrict claims 39 and 51 to wherein the host-compatible cell is derived from the tumor. Specification, claims 51, 45 and 53.

ISSUE

I. WHETHER THE BOARD SHOULD REVERSE THE EXAMINER'S REJECTION OF CLAIMS 39, 45, 51, and 53 UNDER 35USC103.

GROUPING OF THE CLAIMS

Our pending claims shall stand as a group.

ARGUMENT

I. THE BOARD SHOULD REVERSE THE EXAMINER'S REJECTION OF CLAIMS 39, 45, 51, and 53 UNDER 35USC103.

Diefenbach et al. (2000, Nature Immunol. 1(2):119-26) discloses two murine ligands, H-60 and Rae1β, as ligands for the murine NKG2D receptor. In particular, the authors report the identification of these ligands by labeled in vitro binding assays (Figs. 1 & 2) and their expression cloning (Fig. 3). The authors also used NKG2D-specific antibodies to report NKG2D expression on several cell types in vitro (Figs. 4 & 5). The authors also report that COS-7 cells (an African green monkey kidney fibroblast cell line transformed with SV-40 virus) transiently transfected to express the ligands can be stained with NKG2D, and that these NKG2D labeled cells can induce lysis and IFN production by NK cells (Fig. 6), and NO and TNF production by macrophages (Fig. 7), all in vitro.

Diefenbach is a publication by the inventors, so they are intimately familiar with its contents. Yet, despite our informed admonitions, the Action continues to misrepresent this reference, manufacturing attributions to coincide with our claims.

At the outset, the Action falsely states that Diefenbach teaches expression of mulivalent NKG2D ligands to [sic] a host compatible *tumor* cell, citing Abstract; p.121, Fig.3b caption; p.121, bridging para of col.1 and 2. Action, p.3, lines 20-22. Diefenbach does not express the ligands in a *tumor* cell – Diefenbach expresses the ligands in COS-7 cells. COS-7 is an African green monkey kidney fibroblast cell line transformed with SV-40 virus – it is not a tumor cell, and Diefenbach no where calls it a tumor cell. The Action introduces the word "tumor" to make it sound like Diefenbach has something to do with targeting tumors, which it does not.

Next the Action states that Diefenbach also teaches target cell killing, and that this effect in and of itself is regarded as effective inhibition of tumor growth, citing p.123, Fig.6; p.123, col.1 and first sentence of col.2. Action, p.3, line 22 - p.4, line 3. This remarkable allegation – that Diefenbach teaches the effective inhibition of tumor growth – is as deceptive as it is false. Diefenbach teaches nothing about inhibiting tumor growth. There is no tumor in Diefenbach to inhibit. Furthermore, the cited target cell killing is that which we describe above: Diefenbach reports that COS-7 cells transiently transfected to express the ligands can be stained with NKG2D, and that these NKG2D labeled cells can induce lysis and IFN production by NK cells (Fig. 6), and NO and TNF production by macrophages (Fig. 7), all in vitro. Our claims have nothing to do with these in vitro methods of decorating ligand-transfected cells with NKG2D. The Action deceptively alleges a teaching of tumor growth inhibition, and then cites unrelated and unsupporting ligand expression experiments in Diefenbach.

Next the Action misleadingly points to *the multivalent system* taught by Diefenbach stimulating cytotoxicity and IFN-γ by natural killer (NK) cells and TNF-α and nitric oxide production by activated macrophages, suggesting a general role of the NKG2D-ligand system in innate immunity. Action, p.4, lines 3-7. What multivalent system? Diefenbach never mentions "multivalent" anything. By avoiding detail, the Action can juxtaoppose words from our claims with unrelated results in Diefenbach. Our claims inhibit tumor growth by administering a *multivalent NKG2D-binding agent comprising a plurality of non-covalently linked NKG2D-*

binding moieties of natural NKG2D MICA, MICB and ULBP ligands, wherein the moieties are restricted to a common presenting surface of a host-compatible cell transduced to express the binding moieties. Does Diefenbach use any such multivalent system? Of course not ... the only multivalent anything of Diefenbach are the mNKG2D tetramers used to stain the H-60 and Rae1β transfected cells. Fig.6(a) shows that cells transfected with H-60 or Rae1β and decorated with the NKG2D tetramers were more efficiently lysed than non-transfected cells, and that the lysis was reduced by the presence of NKG2D antiserum. Where in Diefenbach is anything suggestive of our administration to a cancer-afflicted host of a multivalent NKG2D-binding agent comprising a plurality of non-covalently linked NKG2D-binding moieties of natural NKG2D MICA, MICB and ULBP ligands, wherein the moieties are restricted to a common presenting surface of a host-compatible cell transduced to express the binding moieties?

The Action concludes that Diefenbach teaches that production of a tumor cell encompassing multivalent NKG2D could be done and would be efficient in an in vivo setting because of the ease and efficiency of making the said cells, as well as the art-established fact that NKG2D ligands play a role in innate immunity. Action, p.4, lines 7-10. Diefenbach teaches nothing about tumor cells. Putative ligands of the NKG2D receptor were previously identified in human cells, and Diefenbach adds to that knowledge by identifying two putative NKG2D receptor ligands in murine cells. There is nothing in Diefenbach that suggests that multivalent NKG2D-binding agents could be used to inhibit tumor growth. There is nothing in Diefenbach that suggests or even relates to inhibition of tumor growth. The Action's proposal that Diefenbach's experiments with ligand-transfected Cos-7 cells teach an efficient, in vivo therapy, is unsupported and facially incredible.

WO 98/19167 describes immuno-detection of chimeric MICA proteins (Example 1), generation of mice transgenic in human MICA (Example 2), genetic analysis of the allelic repertoire of MICA (Example 3), and binding of T cells to cells transfected to express MICA (Example 4). From these findings, WO 98/19167 proposes that MICA and MICB could be used as markers for cancer (p.3, line 18 - p.4, line 17; as reagents for isolating, enriching or expanding certain T-cells (p.4, line 18 - p.5, line 12; p.5, line 26 - p.6, line 3); as targets for therapy with anti-MICA and anti-MICB antibodies (p.5, lines 13-25); and to increase or decrease MICA or

MICB expression (p.6, lines 4-15). There is nothing in WO 98/19167 that suggests that administered multivalent NKG2D-binding reagents could be used to inhibit tumor growth. As with Diefenbach, the Action misrepresents this reference.

The Action states that the WO document provides a method of increasing MICA or MICB on tumor cells to treat cancer, citing p.5, lines 13-25; p.6, lines 4-12, and p.57, lines 9-16. The first citation is a Summary paragraph which purports to disclose a method of using a MICA- or MICB-binding agent, such as an anti-MICA or anti-MICB antibody, to target a tumor cell expressing MICA or MICB on its surface. The second citation is a Summary paragraph that proposes increasing MICA or MICB expression, such as with a viral expression vector, and the third citation is a detailed description of this proposal, suggesting that the MICA or MICB could be delivered directly to the cell as proteins, or more practically, as expression constructs. The immediately preceding paragraph (p.57, lines 4-8) explains that this embodiment may be used where an aberration in the gene product or expression is not sufficient for normal function, and that this allows for the alleviation of symptoms of biological disorders experienced as a result of allelic mutation in MICA or MICB.

With respect to therapy, WO 98/19167 proposes that you can target MICA or MICB expressing cells with anti-MICA and anti-MICB antibodies, and that you can increase MICA or MICB expression, or block MICA or MICB expression (p.57, lines 17-21) in cells which under- or mis-express these proteins. Our claims do not target MICA or MICB expressing cells, and we do not modulate target cells which under- or mis-express MICA or MICB. We are not administering anti-MICA or anti-MICB antibodies, and we are not administering to any host MICA or MICB proteins or expression vectors. We are administering multivalent NKG2D ligands, which may include MICA or MICB, on the surface of a host-compatible cell transduced to express the binding moieties. In our claims, the therapy is a transduced cell. Nowhere does WO 98/19167 suggest administering any transduced cells as any therapy, let alone the specifically recited cells and therapies of our claims.

As pointed out in our Specification, several distinct families of cell surface ligands for NKG2D, such as MICA and MICB have been identified. These ligands are often expressed at high levels by tumor cells, but not by normal cells in mature animals. That is why the WO

98/19167 proposes using MICA- and MICB-binding agents to target cancer cells. However, the very prevalence of these ligands on highly tumorigenic cells suggested that their presence is insufficient to provoke a host rejection of the tumor (Specification, p.1, lines 22-30), which teaches away from the presently claimed invention, wherein multivalent NKG2D ligands have been shown to provide immunotherapeutic agents to inhibit tumor growth in situ.

Appellants respectfully request reversal of this rejection. We petition for and authorize charging our Deposit Account No.19-0750 all necessary extensions of time. The Commissioner is authorized to charge any fees or credit any overcharges relating to this communication to our Dep. Acct. No.19-0750 (B01-088-1).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP

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CLAIMS ON APPEAL

1-38. (Canceled)

39. A method for inhibiting prostate tumor growth in a mammalian host determined to have a metastatic prostate tumor and comprising prostate tumor cells expressing native NKG2D, the method comprising steps:

administering to the mammalian host a composition comprising an NKG2D-binding agent, wherein the NKG2D-binding agent is multivalent and comprises a plurality of non-covalently linked NKG2D-binding moieties of natural NKG2D ligands, wherein the moieties are restricted to a common presenting surface, wherein the common presenting surface is of a host-compatible cell transduced to express the binding moieties, wherein the natural NKG2D ligands are selected from the group consisting of MICA, MICB and ULBP, wherein the administering step is effective to inhibit growth of the tumor; and

detecting a resultant inhibition of growth of the tumor by evaluating growth of the tumor.

40-44. (Canceled)

45. The method of claim 39, wherein the host-compatible cell is derived from the tumor.

46-50. (Canceled)

51. A method for inhibiting primary mammary tumor growth in a mammalian host determined to have a primary mammary tumor and comprising mammary tumor cells expressing native NKG2D, the method comprising steps:

administering to the mammalian host a composition comprising an NKG2D-binding agent, wherein the NKG2D-binding agent is multivalent and comprises a plurality of non-covalently linked NKG2D-binding moieties of natural NKG2D ligands, wherein the moieties are restricted to a common presenting surface, wherein the common presenting surface is of a host-compatible cell transduced to express the binding moieties, wherein the natural NKG2D ligands

are selected from the group consisting of MICA, MICB and ULBP, wherein the administering step is effective to inhibit growth of the tumor; and

detecting a resultant inhibition of growth of the tumor by evaluating growth of the tumor.

52. (Canceled)

53. The method of claim 51, wherein the host-compatible cell is derived from the tumor.

54. (Canceled)